Quantifying Variability and Uncertainty with PBPK Models

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“Default” vs. “Model” Uncertainty

- “Default” Uncertainty:

  - Uncertainty regarding the appropriate risk assessment approach to use for a specific chemical due to lack of chemical-specific data

  - Addressed by use of conservative default approach and/or uncertainty factors

  - Difficult to quantify in absence of chemical-specific information

- “Model” Uncertainty:

  - Uncertainty in a chemical-specific risk assessment due to limitations of the available data/model

Mode-of-Action Directed Risk assessment Under the New EPA Cancer Guidelines

<u>Qualitative Information</u>

<u>Quantitative Tools</u>

Mode of Action

- *critical processes leading to cancer*

Tissue Dose Measures

- *chemical moiety and metric most directly related to response*

Selection of Default Extrapolation Approach

Pharmacodynamic (Dose-Response) Modeling

- *relates tissue dose to response*

Pharmacokinetic (Dosimetry) Modeling

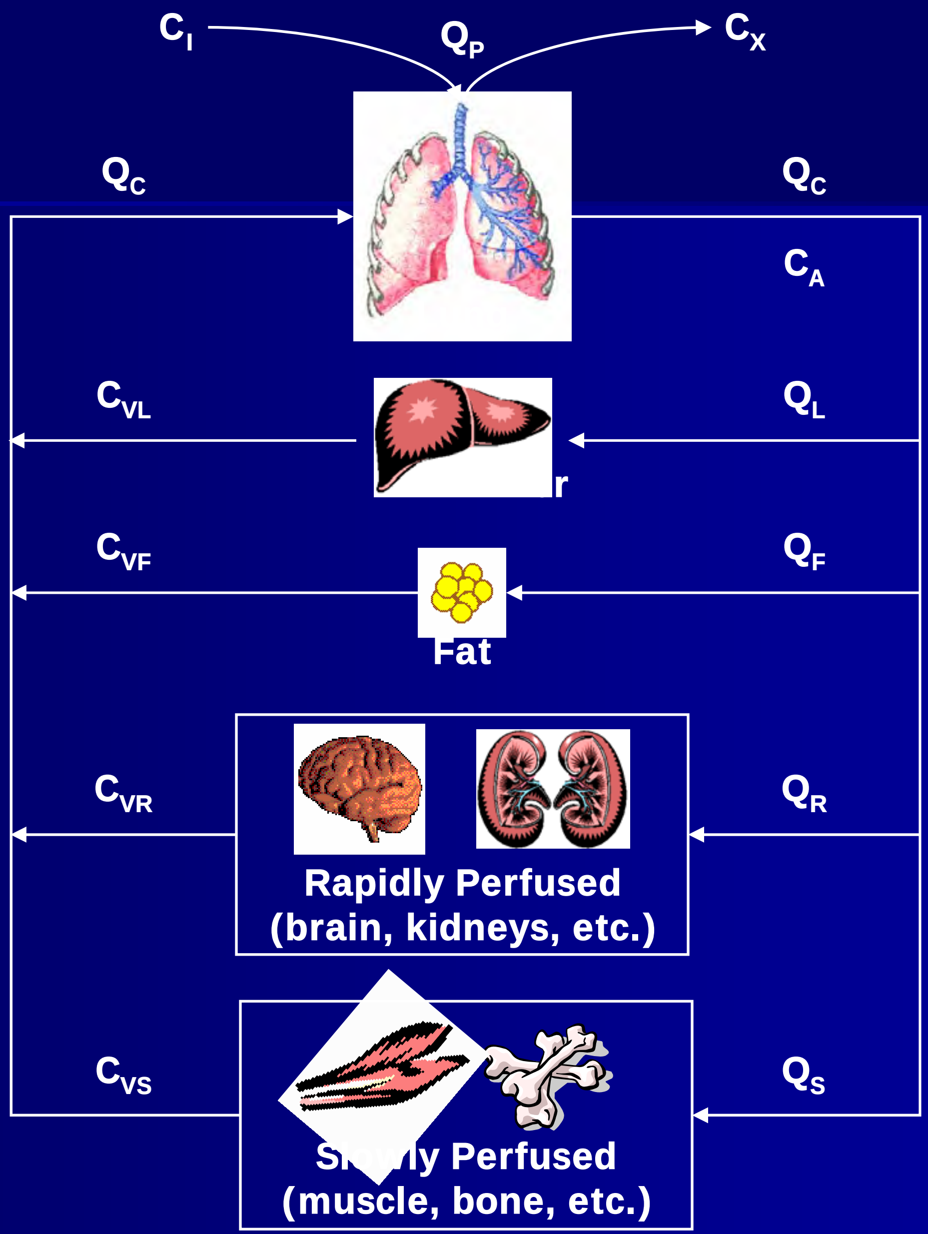
- *relates exposure to tissue dose*

Dosimetric Implementation of Default Approach

Biologically Based Model

Nonlinear Extrapolation Approach

Physiologically Based Pharmacokinetic Model



Physiologically Based Pharmacokinetic Model

Basis of Description

- Model structure
  - anatomy
  - metabolism / transport processes
- Model parameters
  - physiological data (organ weights, blood flows)
  - biochemical data (partition coefficients, metabolism)
- Model equations
  - system of mass-balance differential equations
  - one equation for each tissue
  - connected by equation for blood

Metabolizing Tissue (e.g., Liver):

$$dA_L / dt = Q_L \times \left(C_A - C_L / P_L\right) - V_{\max} \times C_L / P_L / \left(K_M + C_L / P_L\right)$$

Approaches for Evaluating Model Uncertainty

- Uncertainty Regarding Model
  - Comparison of predictions
  - Monte Carlo uncertainty analysis
  - Sensitivity analysis
- Uncertainty Regarding Mode of Action
  - Decision tree analysis

Evaluation of Uncertainty in Model Structure

Comparison of Liver Cancer Dose Metrics* Calculated with Alternative PBPK Models for TCE

Model	**Dose Metric Value***	
	Mouse	Human
	(1000/2000 mg/kg/d)	(1 ug/L)
Clewell	1028/1227	0.014
Clewell/Bois * *	1052/1350	0.004
Fisher	1132/1998	0.006
Fisher/Bois * *	5635/5964	0.004

* Area under the curve for trichloroacetic acid in plasma (Clewell) or liver (Fisher)

* * Recalibration using MCMC

Uncertainty in TCE Lung Tumor Dose Metrics

Using Alternative Possibilities for Cross-Species Scaling of Alcohol Dehydrogenase in lung

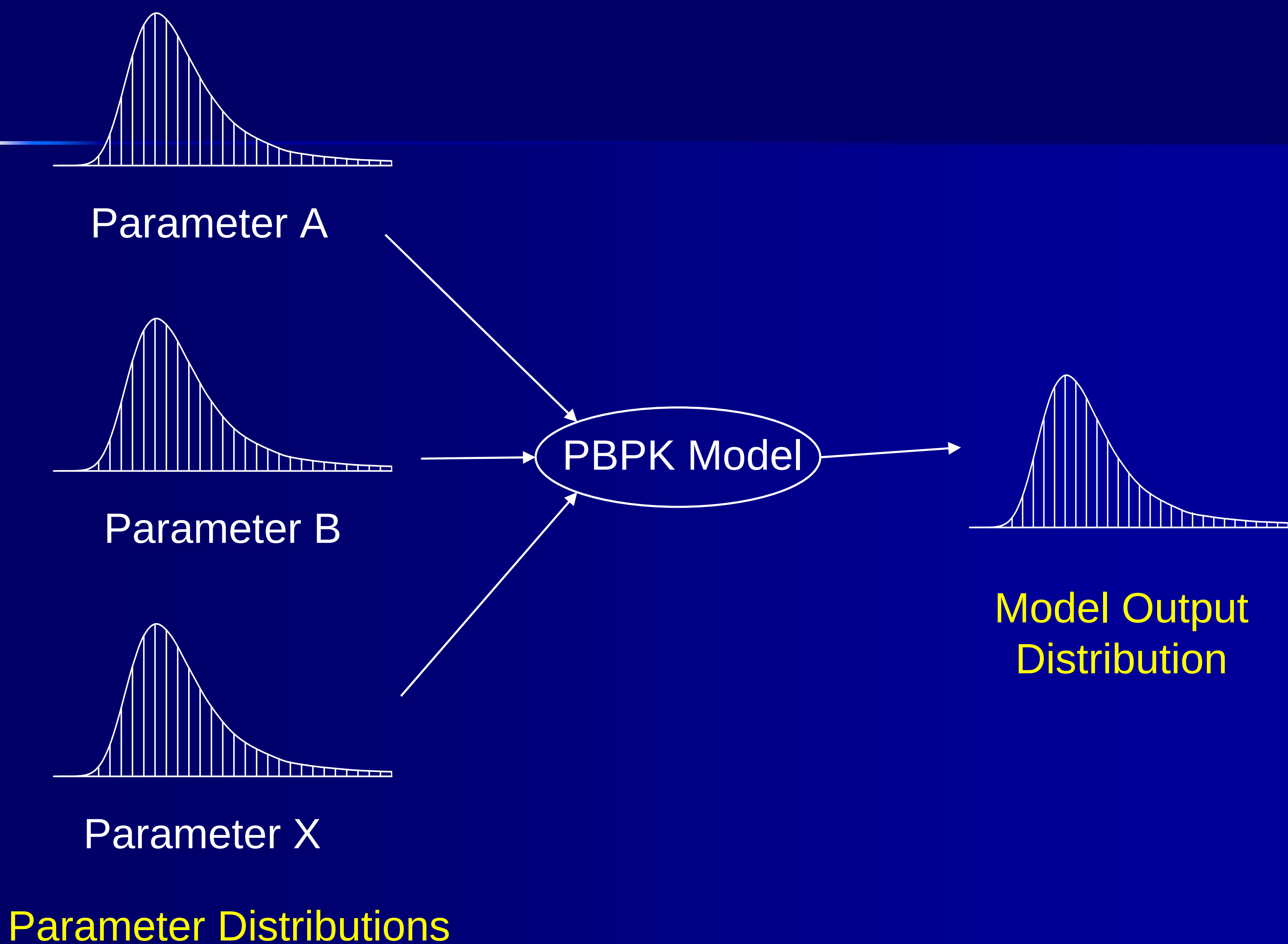
Species / Exposure	Chloral in Lung Tracheobronchial Region	
	AUC	**C_{MAX}**
mouse / 600 ppm*	9.4	2.6
rat / 600 ppm	2.8[a] (28)[b]	0.3 (3.4)
human / 100 ppm	0.016 (10.5)	0.003 (2.2)
human / 1 mg/L	0.00002 (0.01)	--

* Significantly increased lung tumors

[a] Assuming ADH scales by body weight to the ¾ power

[b] Assuming ADH scales similarly to lung P450

Monte Carlo Uncertainty Analysis



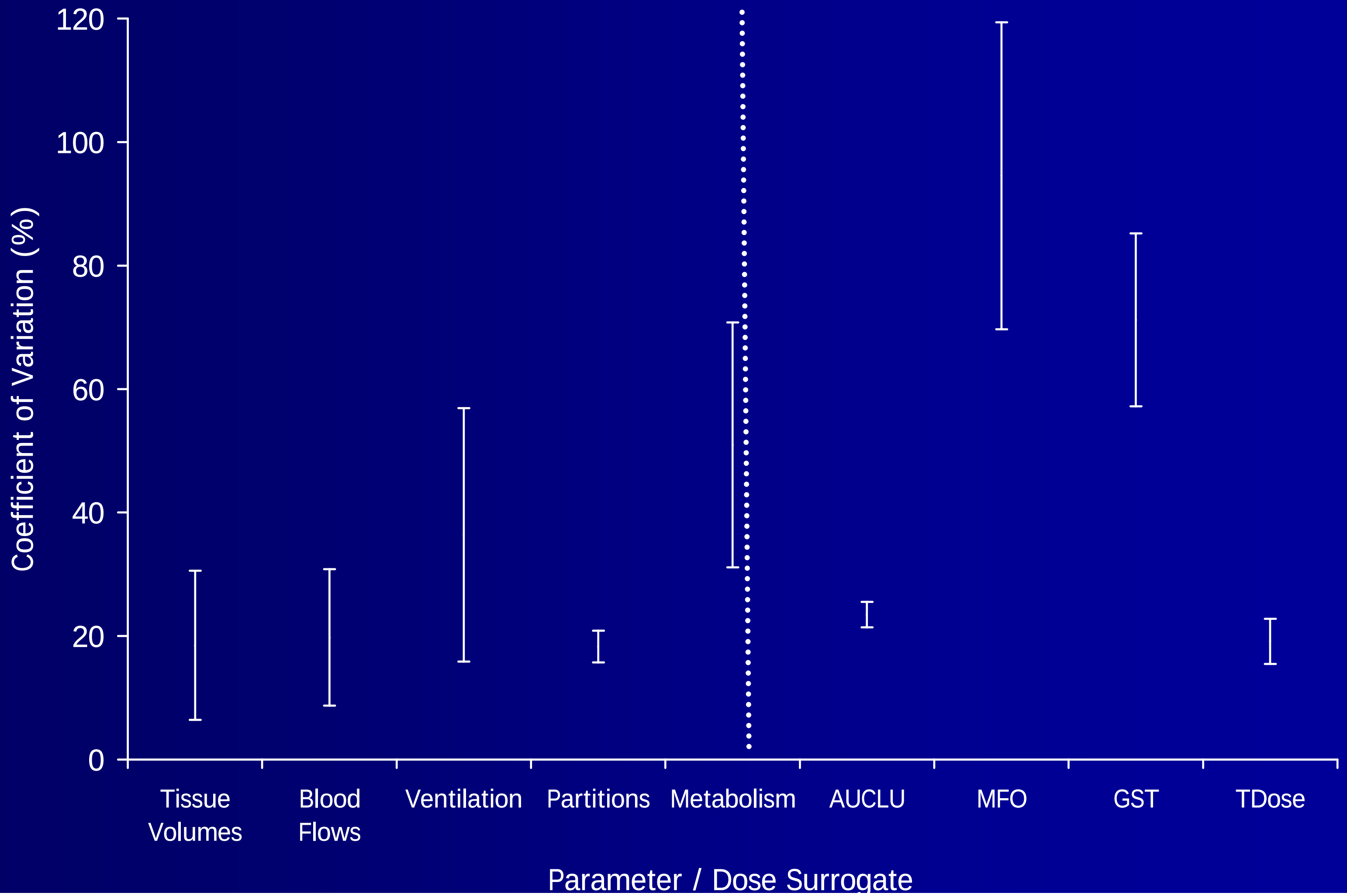
Monte Carlo Uncertainty Analysis

Uncertainty in Noncancer Dose Metrics Calculated with a PBPK Model for Chloropentafluorobenzene

Endpoint	Ratio of Dose Metric Estimates	
	Mouse (50%/5%)	Human (95%/50%)
Hepatotoxicity (AUC)	1.6	1.5
Neurotoxicity (C_{MAX})	1.4	1.3
Fetotoxicity (AUC)	2.5	1.3
Fetotoxicity (C_{MAX})	2.7	1.3

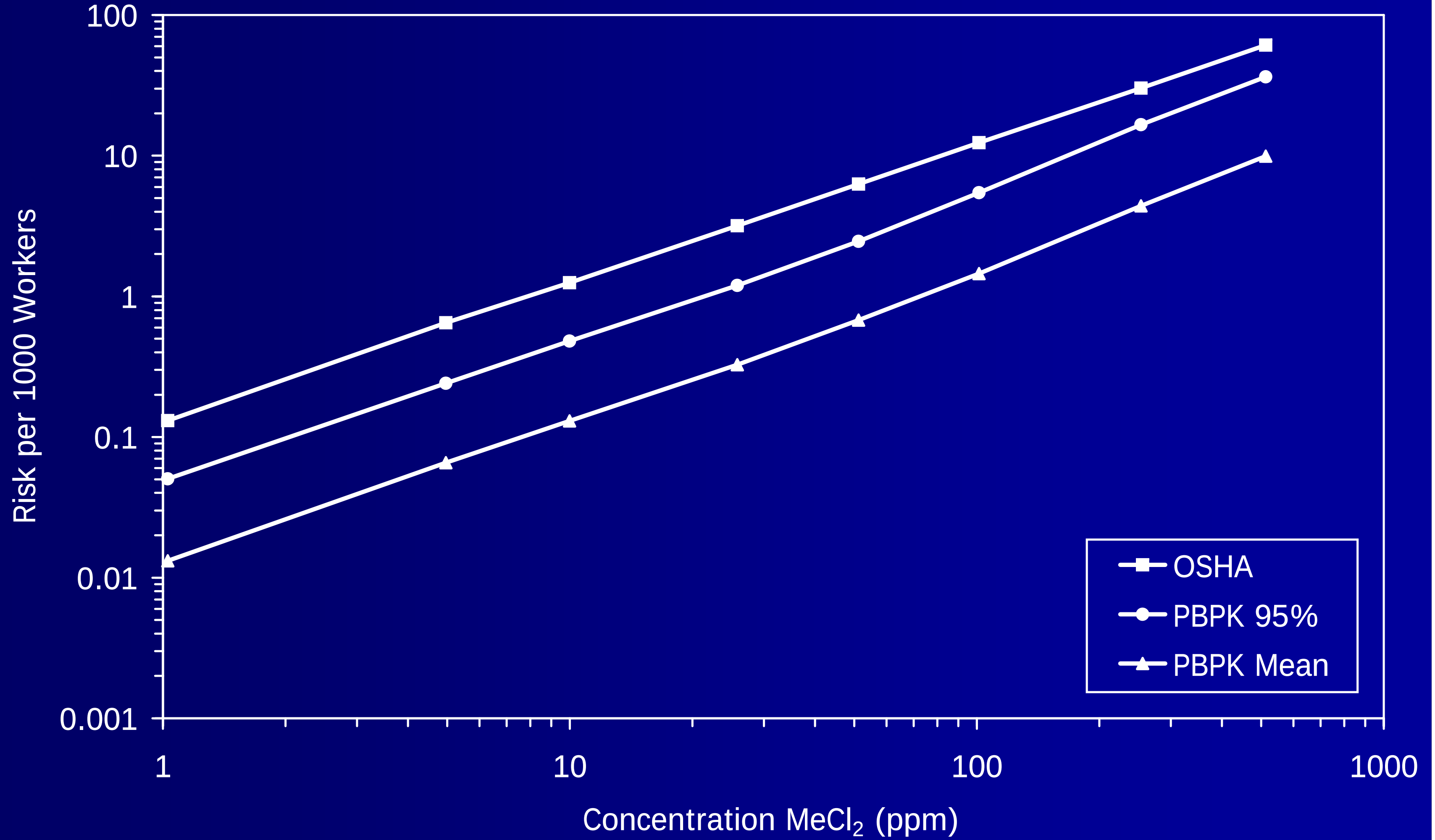
Monte Carlo Uncertainty Analysis

Methylene Chloride Model Inputs vs. Outputs



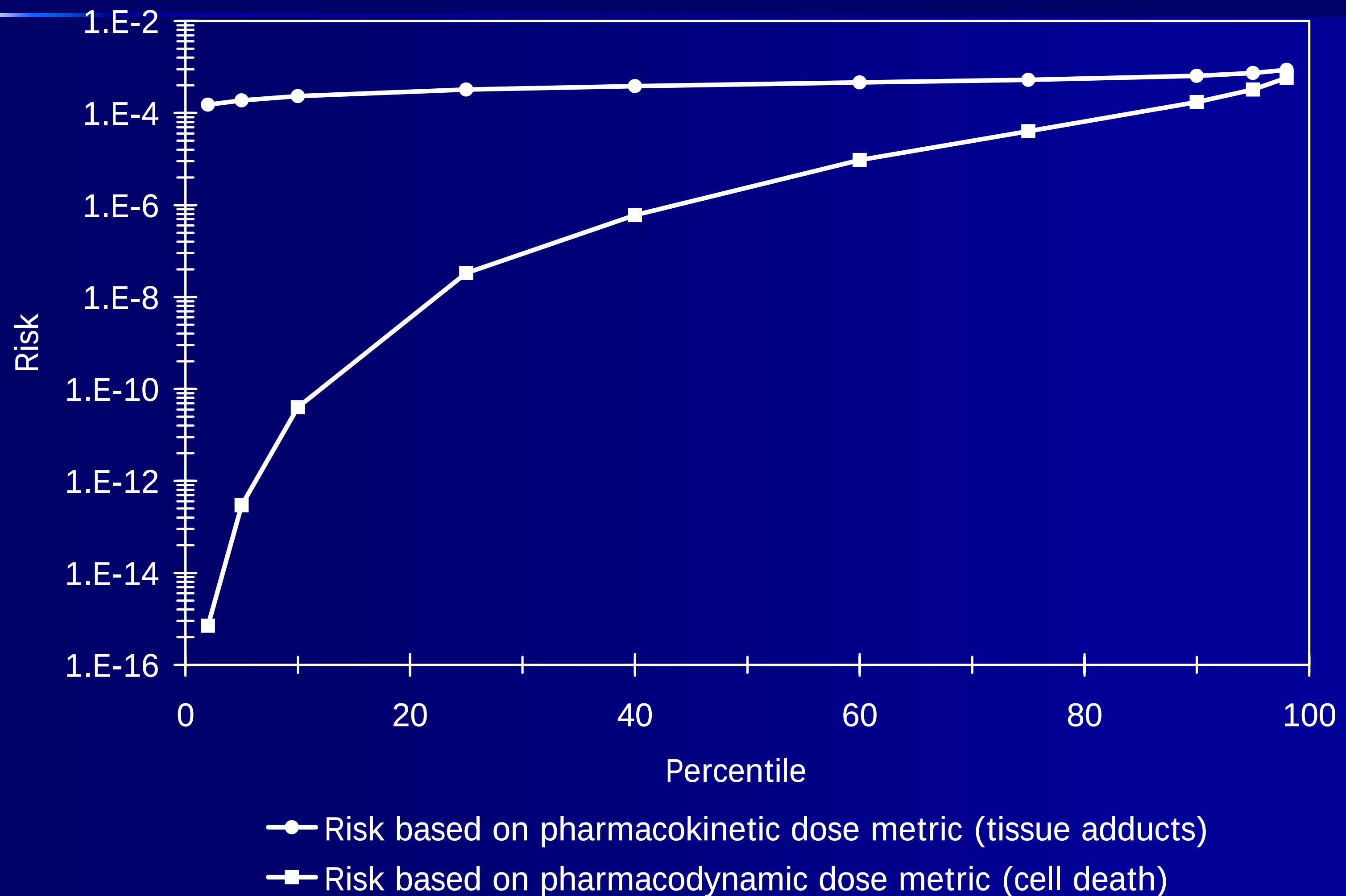
Characterizing the Impact of Model Uncertainty

Comparison of Risk Estimates for Occupational Exposure to $MeCl_2$



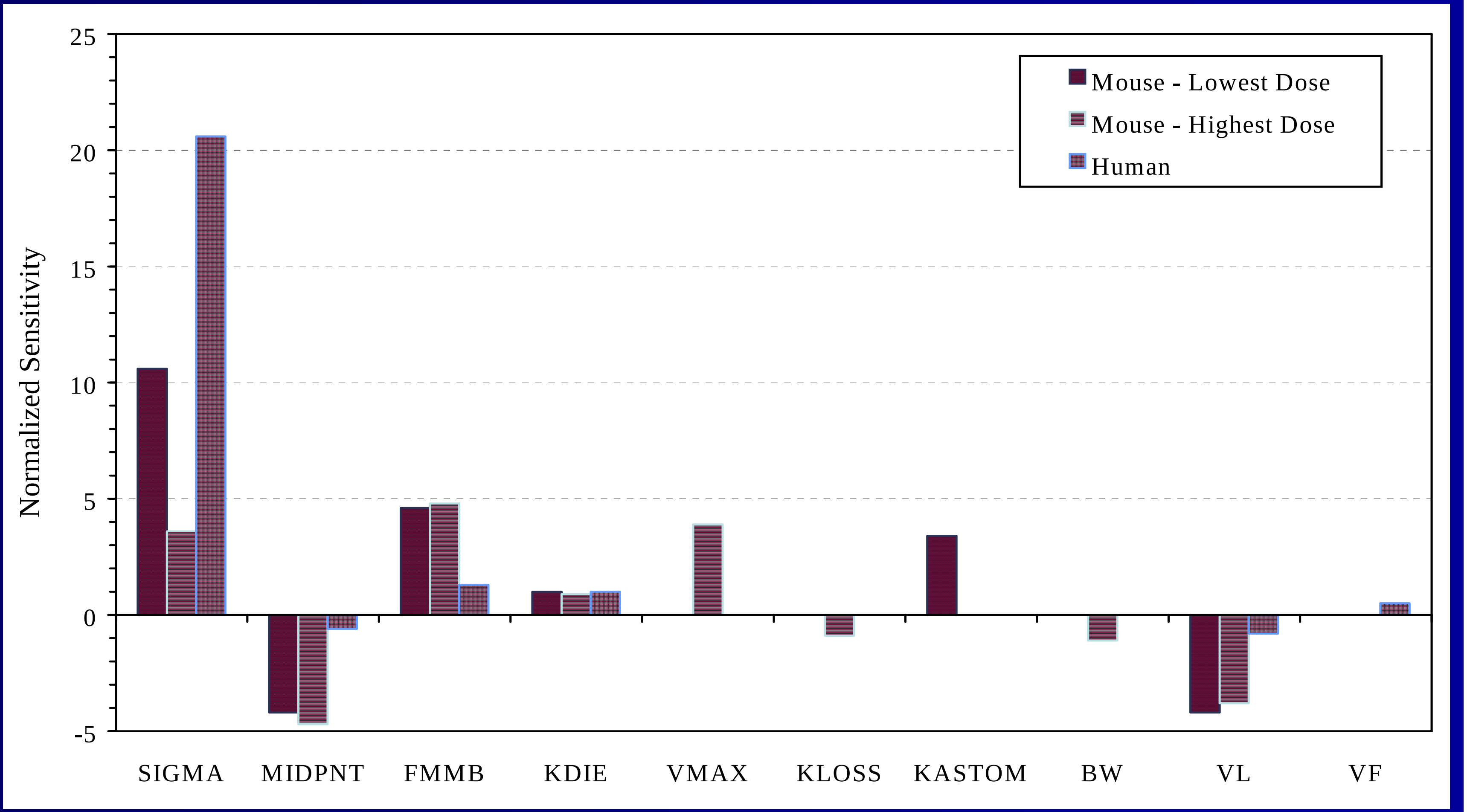
Monte Carlo Uncertainty/Variability Analysis

Distribution of Lifetime Cancer Risk Estimates for Consumption of 1 µg/L Chloroform in Drinking Water



Parameter Sensitivity Analysis

Chloroform Risk Metric (Percent Cell Death)

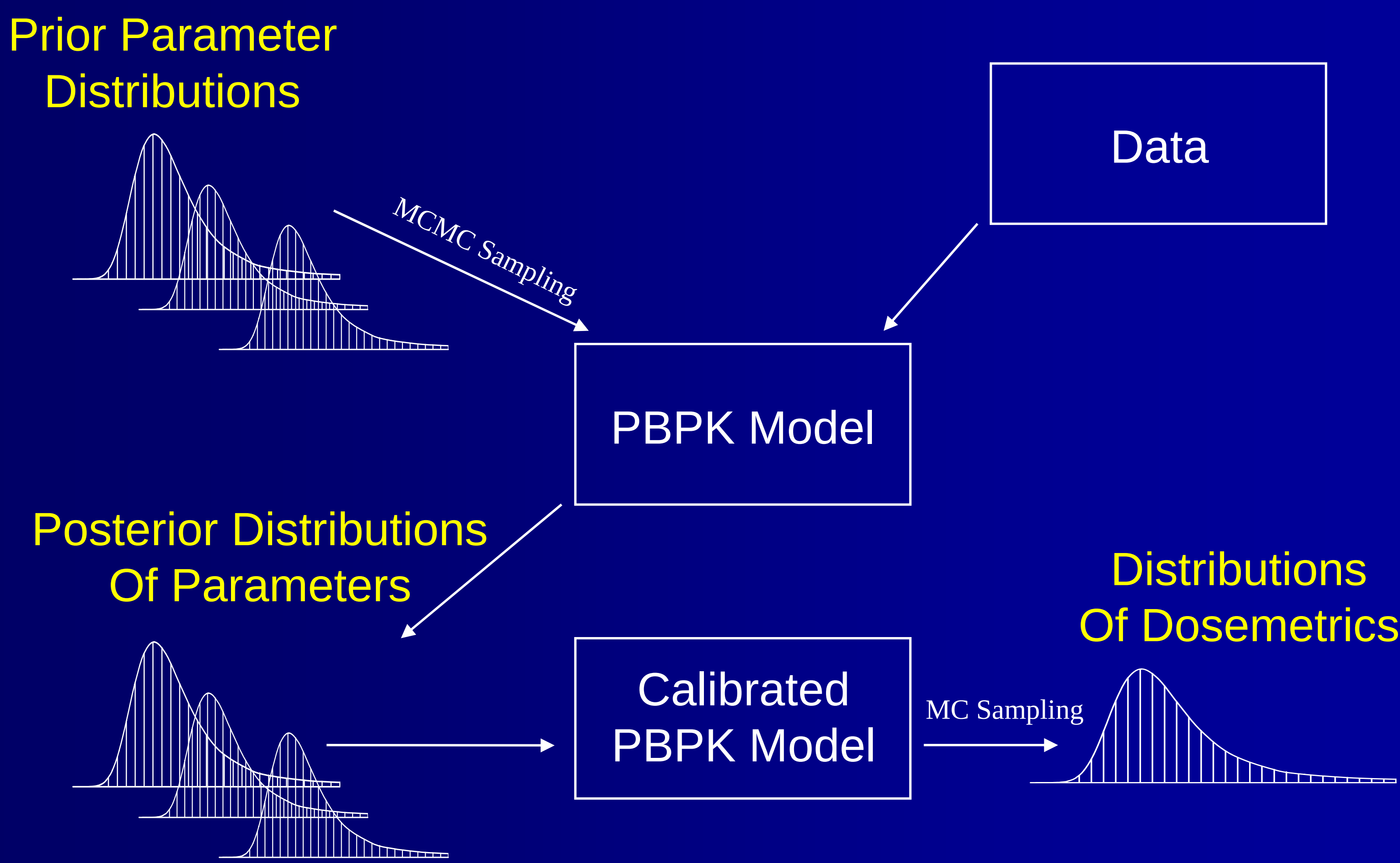


Parameter Sensitivity Analysis

Calculation of Hair Concentration from Ingestion Rate with PBPK Model for Methylmercury

Parameter	Analytical Sensitivity Coefficient	Pearson Correlation Coefficient
BWF	0.24	0.19
kfi	-0.13	-0.23
khi	-0.77	-0.66
PG	-0.13	-0.32
PHB	0.22	0.42
VFC	0.08	0.15
VPC	0.02	-0.13
VRBCC	0.02	-0.13
VRemain	0.03	-0.13
VSC	0.09	0.01

PBPK Model "Calibration" Using Heirarchical Bayesian Analysis



MCMC Uncertainty/Variability Analysis

Comparison of 50th and 95th Percentiles of the Distribution for Risks Predicted with a PBPK Model* for TCE

Target tissue / metric	Risk Ratio (95%/50%)
Liver / TCA	7
Liver / DCA	8
Kidney / DCVC	37
Lung / Chloral	60

* Model of Clewell et al. (2000) with posterior parameter distributions from Markov Chain Monte Carlo Analysis performed by Bois (2000)

Approaches for Evaluating Uncertainty

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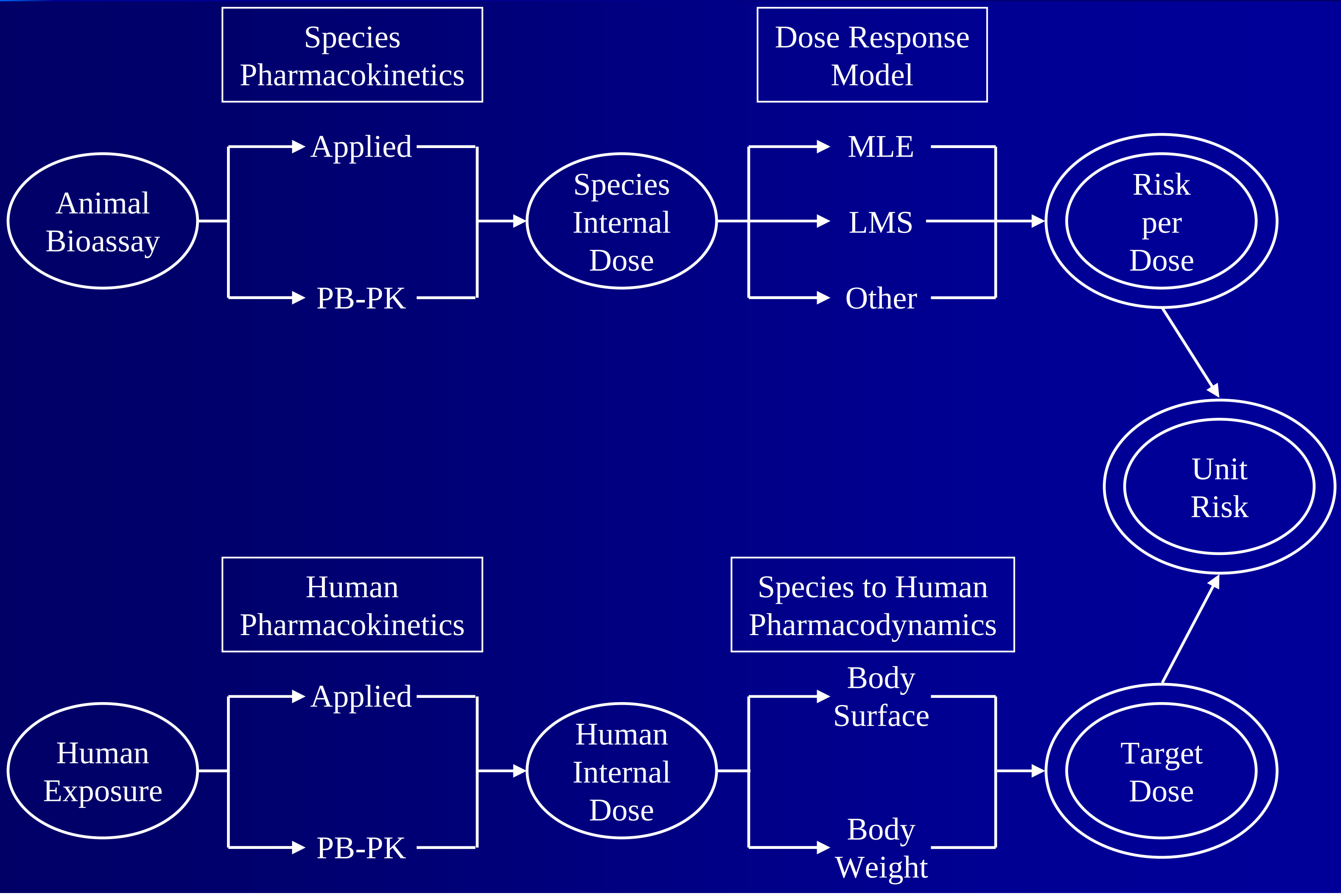
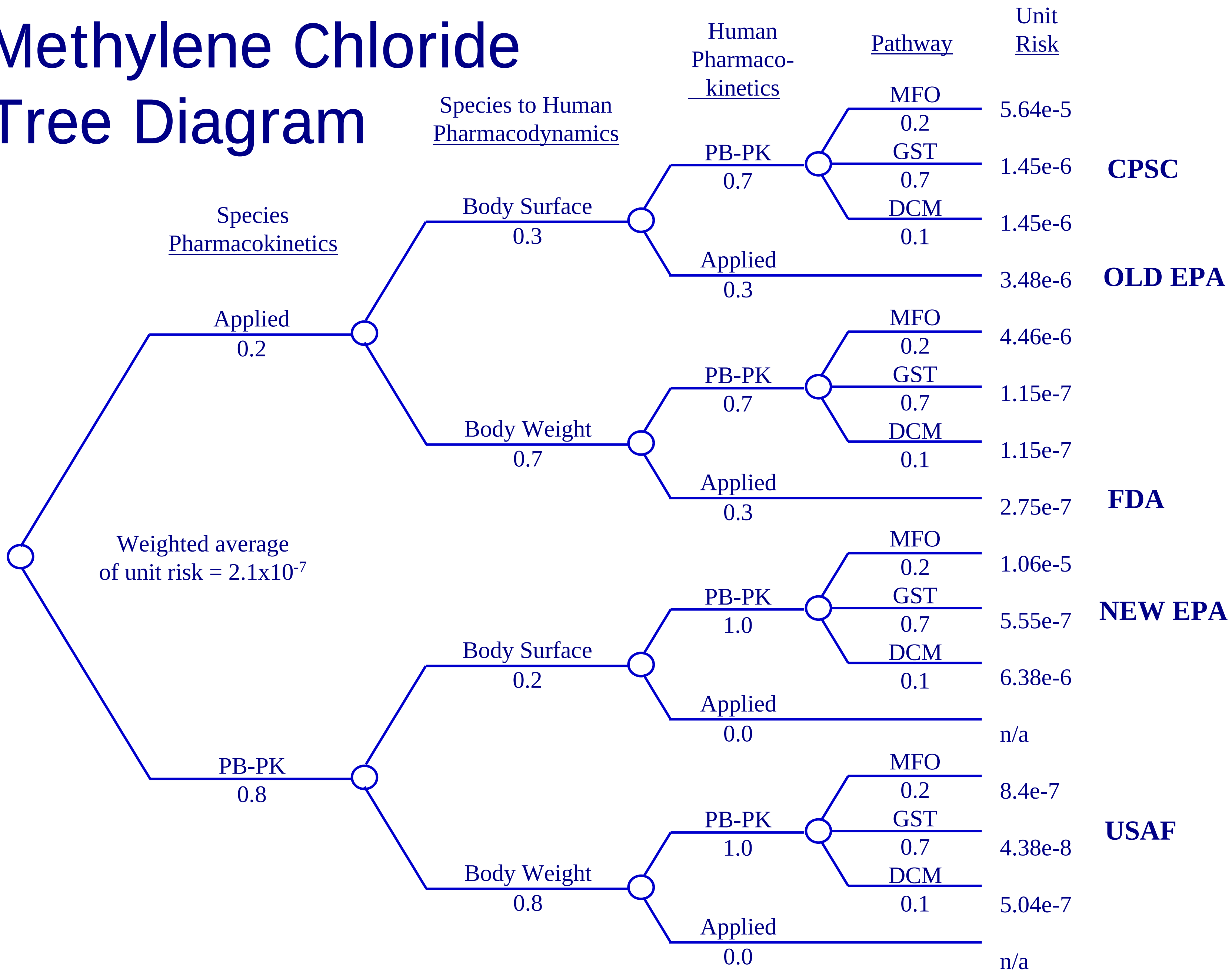
Decision Analysis Framework: Methylene Chloride

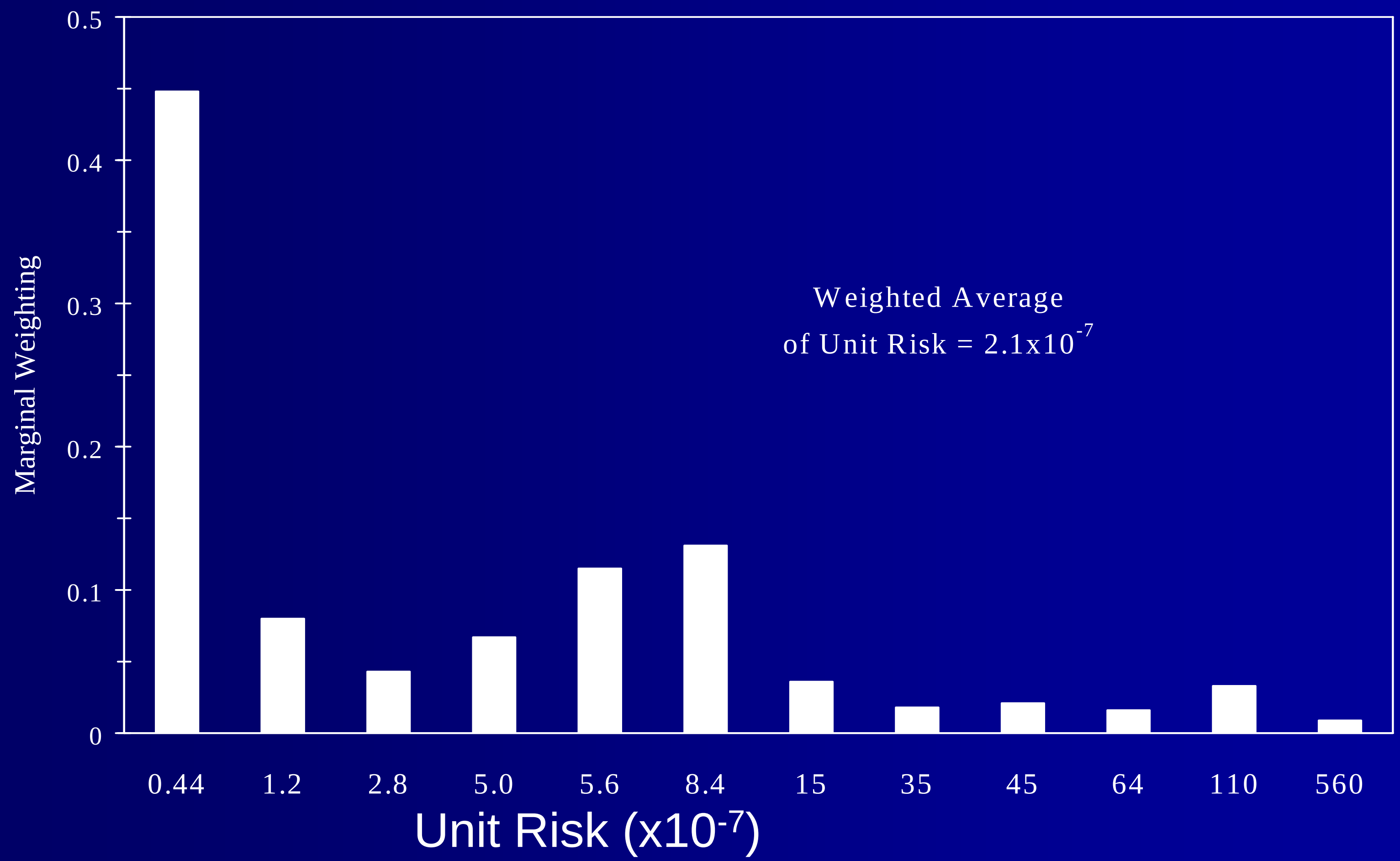


Methylene Chloride Tree Diagram



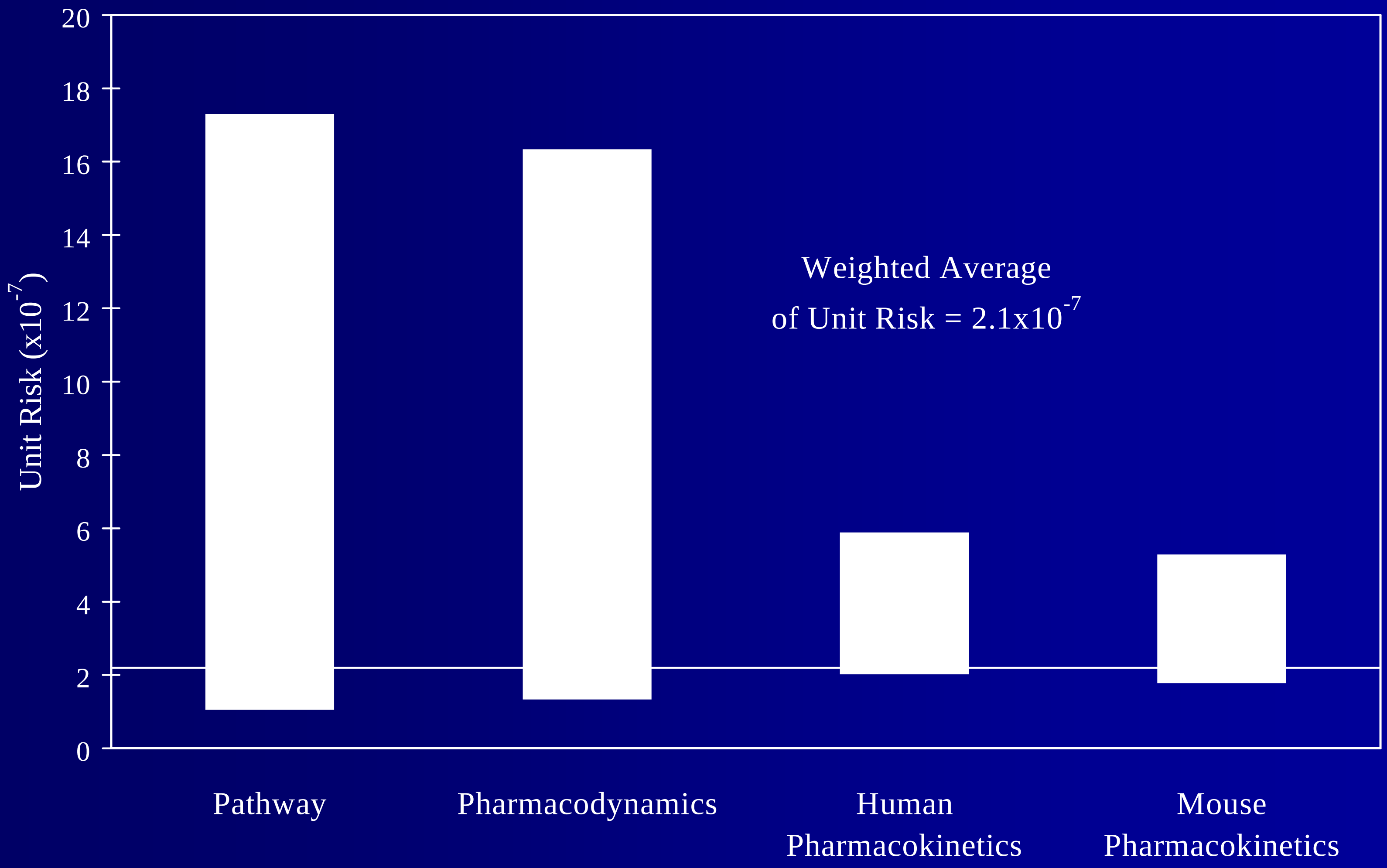
Decision Tree Analysis

Unit Risk Distribution for Methylene Chloride

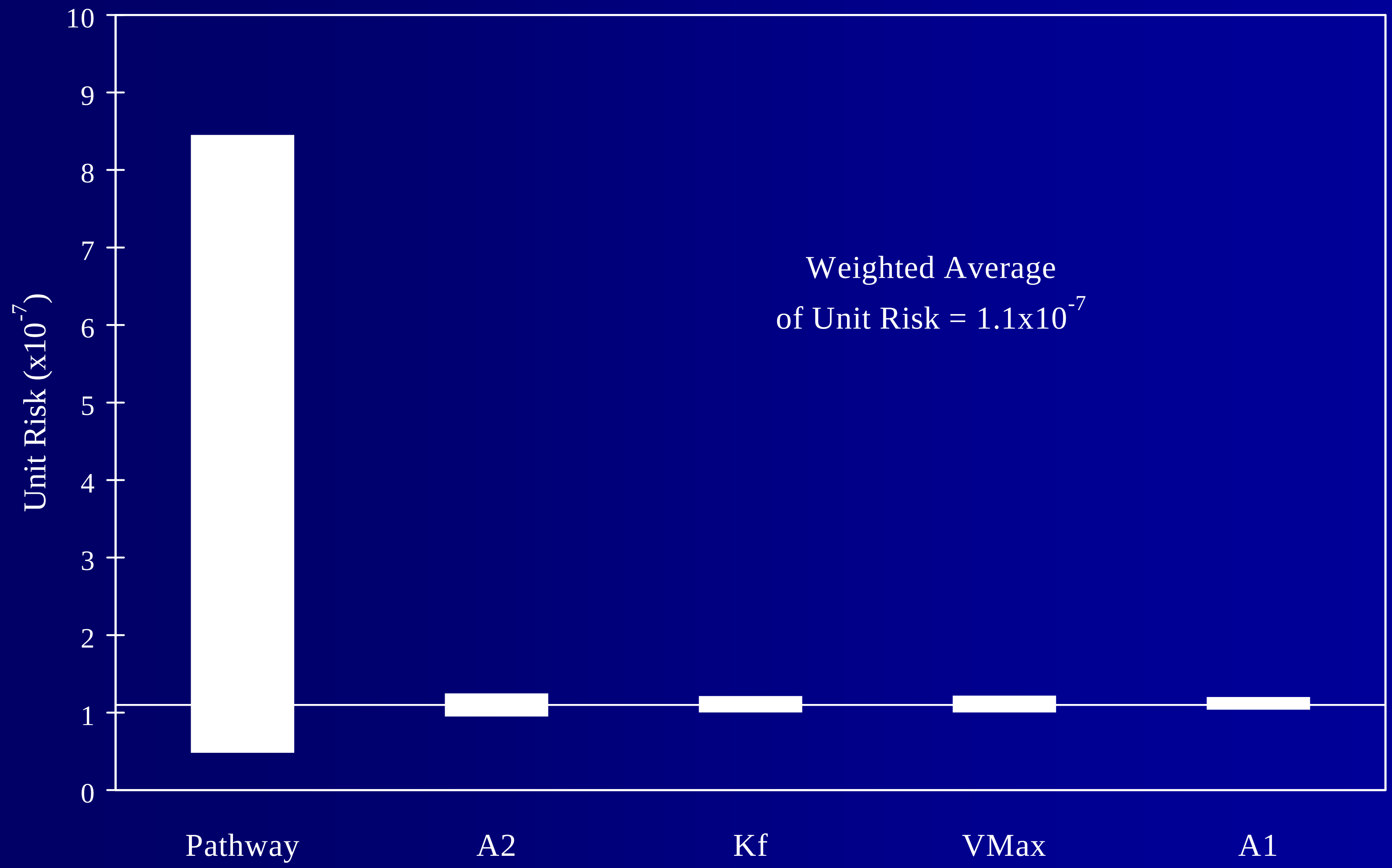


Decision Tree Analysis

Relative Impact of Decisions on Risk



Relative Impact of Decisions vs. Parameter Uncertainty on Risk



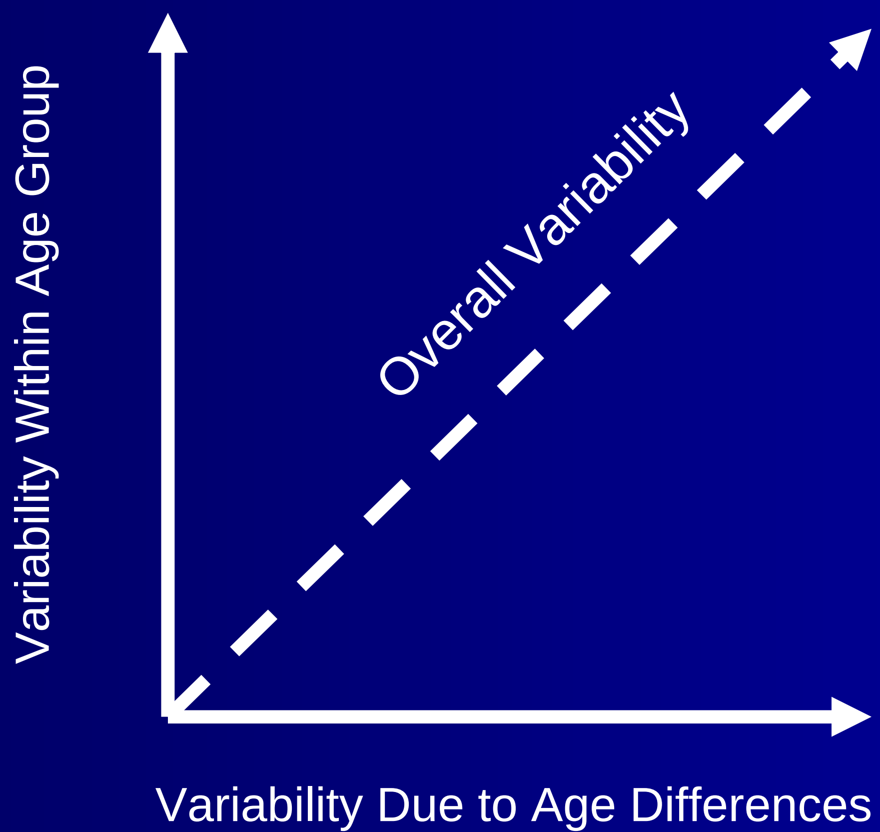
Recommendations *

- When there is uncertainty in estimates of risk, presentation of single estimates of risk is misleading and provides a false sense of precision. Presenting the range of plausible risk estimates, along with a central estimate, conveys a more objective characterization of the magnitude of the risks.

- When risk assessors face model uncertainty, they need to document and disclose the nature and degree of model uncertainty. This can be done by performing multiple assessments with different models and reporting the extent of the differences in results. A weighted average of results from alternative models based on expert weightings may also be informative.

* Source: "Proposed Risk Assessment Bulletin"(OMB, Jan 9, 2006)

Components of Population Variability



Predicting the Potential Impact of Life-Stage Specific Pharmacokinetic Factors on Toxicity

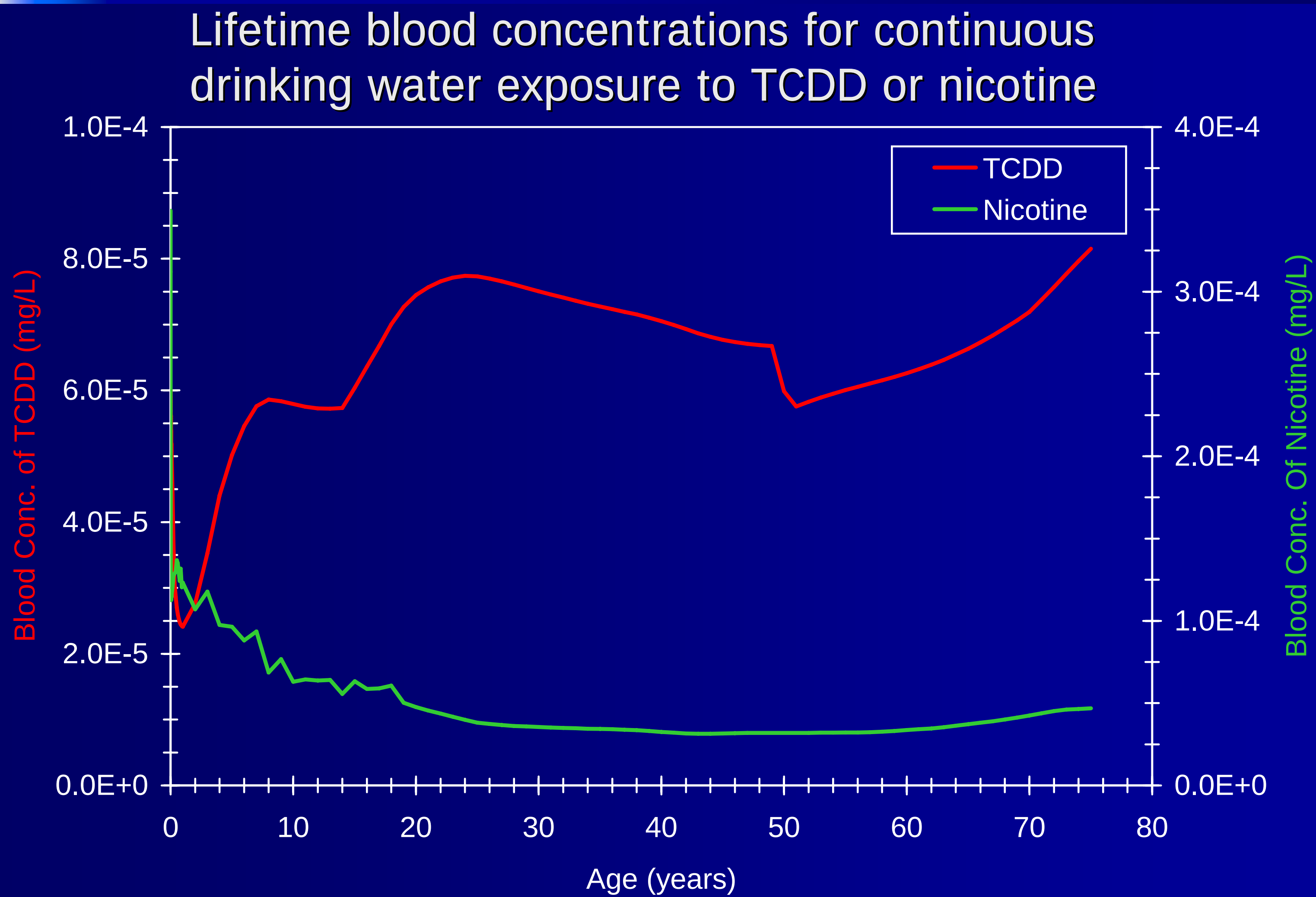
- Assumption: The toxicity of a chemical can be related to some measure of target tissue dose, e.g., the concentration profile of the chemical or its metabolite(s) in the tissue where the effects are produced
- Observation: The relationship of the target tissue dose to the environmental exposure producing it is typically a function of a number of pharmacokinetic factors, each of which can vary across age and gender
- Caution: In addition to pharmacokinetic factors, toxicity during a given life-stage may also be dependent on pharmacodynamic factors (critical periods of development)

Predicting Age-Dependent Pharmacokinetic Sensitivity

- A PBPK model was developed to simulate the physiological and biochemical changes in humans associated with growth and aging.
- All physiological and biochemical parameters were allowed to change with time based on empirical data; only the chemical specific parameters remained constant.

Quantifying Variability

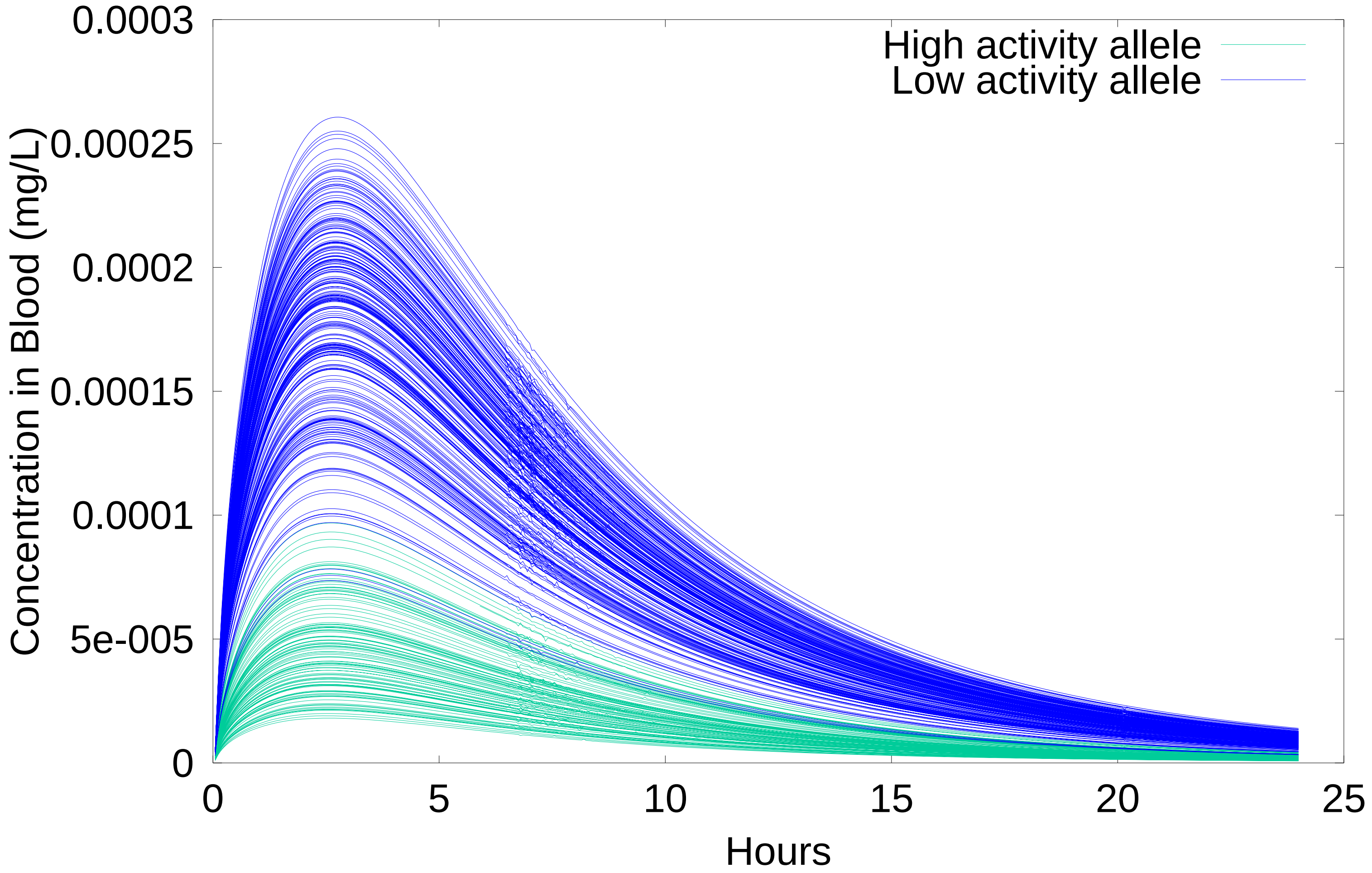
Prediction of Age-Dependent Changes in Internal Dose



Example of Variability Analysis: Paraoxonase Polymorphism

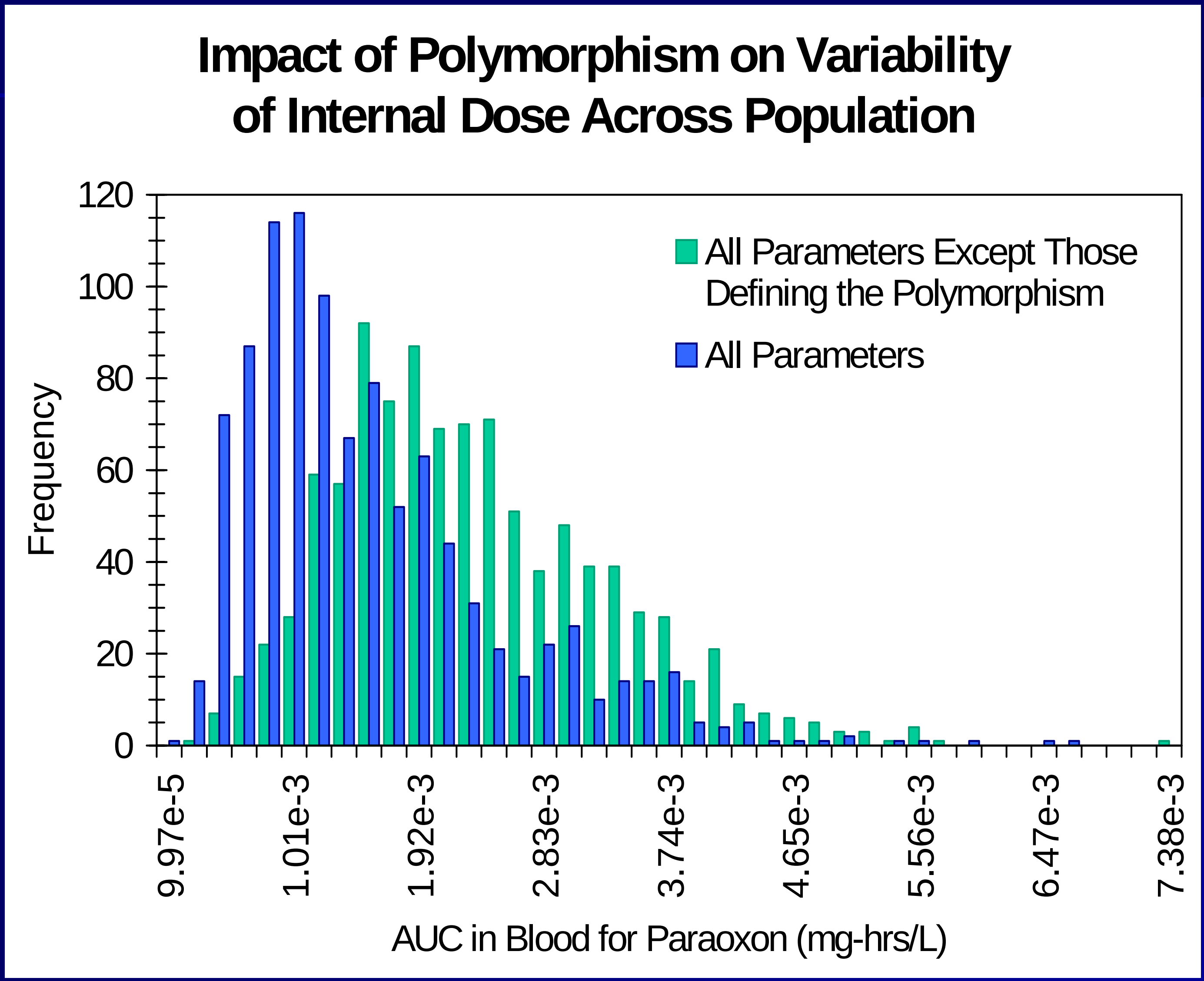
- An existing PBPK model for parathion developed by Gearhart *et al.* (1994) was used. The model includes inhibition of acetylcholinesterase by paraoxon.
- Information on the kinetic differences in the metabolism of paraoxon by the two human alleles of paraoxonase were provided in Mueller *et al.* (1983), Smolen *et al.* (1991), and Davies *et al.* (1996).
- Monte Carlo simulations (1000) were performed to generate input values for the PBPK model, based on the distributions derived from the literature.

Paraoxon Concentration in Blood: High and Low Activity Alleles



Quantifying Variability

Prediction of Impact of Polymorphisms on Internal Dose



Evaluating Pharmacokinetic Variability

- The pharmacokinetic variability across a population is a function of many chemical-specific, genetic, and physiological factors
- Speculation regarding the overall variability in pharmacokinetic sensitivity based on the observed variability of individual pharmacokinetic factors can be highly misleading
- Analysis using a PBPK model and Monte Carlo techniques provides a more reliable approach for estimating population pharmacokinetic variability